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ANTICANCER PROPERTIES OF ZINGIBER OFFICINALE – GINGER: A REVIEW

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ABSTRACT

Carcinogenesis and transformation of a normal cell to tumor is caused by many environmental, lifestyle and biological factors. Cancer incidence and death cases also increased gradually. Developing new, early detection methods, risk assessment, creating awareness on healthy food habits, preventive measures may help in prevention of many diseases including cancer. Providing effective anticancer drugs to treat cancer is one of the major requirements in cancer therapy.

Many plants and their products have active anticancer agents. Ginger is considered as an important spice with many clinical potential activities. Ginger and its compounds display anti-inflammatory, antioxidant, antimetastatic and anticancer agent. The anticancer activity of ginger components is reviewed in this article due to its versatile therapeutic nature.

KEYWORDS: Cytotoxic, Carcinoma, Zinger, Natural Products and Anticancer Drugs, Cancer, Signaling, Medicinal Plants, Inhibitors

INTRODUCTION

Zingeber officinale *(*ginger*)* belongs to Zingiberaceae is an essential spice, condiment and traditional medicine for many human ailments and is used worldwide since ancient period. Indian and Jamaican ginger are considered superior followed by the West African variety. Jamaican ginger possesses delicate and flavor and is sometimes as first grade. Nigerian dried ginger possess a camphorhaceous and a coarser odor and is rich in both aroma and pungency factors. Chinese ginger is low pungency and mainly exported as preserves in sugar syrup or sugar candy (Govindarajan, 1982a, 1982b; Vasala, 2004; Kafer and Milner, 2008)

Ginger root and its main phenolic compounds such as gingerols and zerumbone have anticarcinogenic activity, antioxidant and anti inflammatory activity. Specially, the constituents of ginger root (figure 1) can inhibition of activation of NF-kB induced by a variety of various factors (Shukla and Singh, 2006; Ahmad et al., 2001; Katiyar et al., 1996; Park and Pezzuto, 2002, Surh, 1999- 2008; Manju and Nalini, 2005; Baliga *et al.*, 2011). Ginger candy, ginger bread, biscuits, pickles, and ginger flavoured carbonated drinks (Arctangder, 1960; Bakhru, 1999).

Ginger tea or masala chai is a special tea prepared in India. In India is also considered as one of the traditional cooking spice (Murray, 1995). It is typically consumed as a fresh paste, dried powder and is an indispensable component of curry powder and sauces. Study of the anticancer, antioxidant, and antimycobacterial activities were performed by using the extracts of rosemary (*Rosmarinus officinalis* L.), turmeric (*Curcuma longa* L.) and ginger (*Zingiber officinale* Roscoe). The anticancer activity was tested against nine different types of human cancers. The extract of ginger and turmeric showed anticancer activities (Leal *et al.*, 2003).

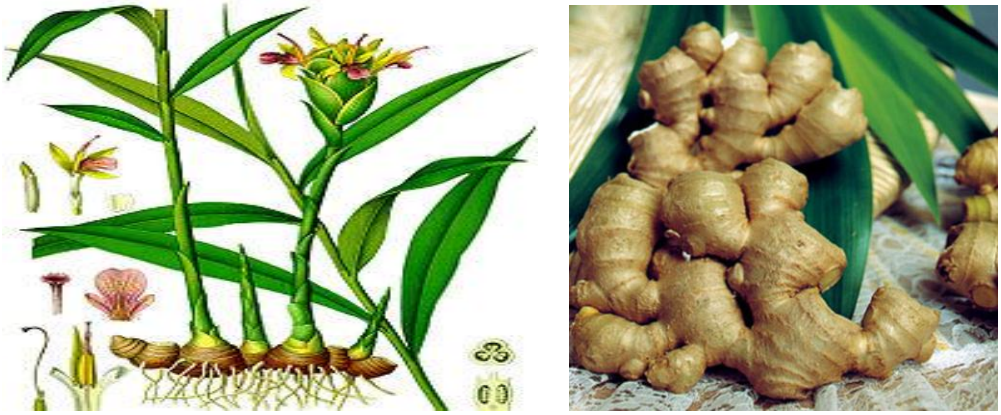

Figure 1: Zingeber Officinale (Ginger) Plant and Ginger Rhizome

Clinical Significance of Ginger

Many of the herbs and spices possess an array of biochemical and pharmacological activities including anti-inflammatory and antioxidant properties that are believed to contribute to their antimutagenic and anticarcinogenic activities (Awang,1992, Bakhru, 1999; Chen et al., 2011; Aggarwal and Shishodia, 2006; Ahmed and Sharma, 1997). The spice ginger contains gingerol, a phenolic substance mainly and has diverse pharmacologic effects such as anti-inflammatory, antioxidant, and anti-apoptotic effects.

Since tumor promotion is closely linked to inflammation and oxidative stress, a compound that exhibits anti inflammatory and/or antioxidant properties could acts as anti-carcinogenic agent (Grzanna et al., 2005, Rhode *et al.*, 2007; Sang *et al.*, 2009; Butt and Sultan, 2011). The ginger has significant role in treating some diseases including gastrointestinal complications, treat stomach upset, diarrhoea, rheumatic disorders, nausea, common colds, fever, and dizziness. And also ginger possesses antineoplastic and chemopreventive properties (Pereira, 2011; Baliga *et al*., 2011).

Chemical Composition of Ginger

Ginger contains two distinct groups of chemicals and they are volatile and non-volatile compounds (Table. 1). The volatile oil components consist mainly of sesquiterpene hydrocarbons, predominantly zingeberene (35%), curcumene (18%) and farnesene (10%), with lesser amounts of bisabolene and b-sesquiphellandrene. A smaller ammount of at least 40 different monoterpenoid hydrocarbons are present with 1, 8-cineole, neral, borneol, linalool, and geraniol being the most abundant and many of these volatile oil components contribute to the distinct aroma and taste of ginger (Govindarajan, 1982). Ginger contains biologically active constituents including the non-volatile pungent principles, such as the gingerols, paradols, shogaols, and zingerone that produce a hot sensation (Shukla and Singh, 2007; WHO 2008).

The ginger contains zingiberene and 6- gingerol being the important constituents in stomachic medications. The gingerols were identified as the major active components in the fresh rhizome and are a series of chemical homologs differentiated by the length of their unbranched alkyl chains, (Govindarajan, 1982). In addition, the shogaols, dehydrated form of the gingerols, are the predominant pungent constituents in dried ginger (Connell and Sutherland, 1969).

Paradol is similar to gingerol and is formed on hydrogenation of shogoal. In addition to the extractable oleoresins, ginger contains many fats, vitamins, carbohydrates, waxes, and minerals. Ginger rhizomes also contain zingibain a potent proteolytic enzyme (Shukla and Singh, 2007).

Table 1: The Chemical Composition of Ginger Rhizome and Uses of Ginger

S No	Chemical Composition (in %)	Volatile Oil Consists: The Monoterpenes & Sesquiterpenes	Non-Volatile Oil Contains	Other Constituents	Uses of Ginger
1	Carbohydrates: 60–70%	1).*α*-farmesene *α*-zingiberene,*β*-bisabolene, *β*-elemene, *β*-phellandrene, *β*-esquiphellandreneborneol , camphene, cineole,curcumene, geraniol,geranyl acetate, limonene,linalool, terpenes, terphineol, zingiberenol zingiberol,	Gingerols, paradols Shogaols, zingerone, (Pungent compounds).	capsaicin, diarylheptanoids,galactosylglycerols, galanolactone, gingediol, ginger protease, gingerglycolipids, gingesulfonic acid, monoacyldi vitamins, neral, phytosterols	Spice, Antioxidant, anti-inflammatory antineoplastic , chemopreventive, antiangiogenic, antimetastatic, activates-apoptosis, anticancer
2	Protein: 9%				
3	Fatty oil: 3–6%		A series of homologs with linear alkyl chains -[3–6]-, [8]-, [10]-,and [12]-gingerols; and having a side-chain with 7–10, 12, 14, or 16 carbon atoms.		
4	Crude fiber: 3– 8%				
5	Ash: 8%				Fever, antipyretic Cold, Antimicrobial, Antischistosomal, Hypoglycaemic, Hepatoprotective, Diuretic, Hypocholesterolenic, Broad spectrum of antihelminthic effect, Heart condition, Rheumatic complaints.
6	Water: 9–12%				
7	Volatile oil : 2–3%				
8	**And also contains**:	2). Sesquiterpene hydrocarbon: *α*-ingiberene (20–30%) of the oil.			
9	Oleoresins, Minerals Potent proteolytic enzyme called Zingibain.				
10 Ref	Govindarajan, 1982a; 1982b; Ali *et al*., 2008.	1.Govindarajan, 1982a; 1982b.	Vasala, 2004;	Shukla and Singh, 2007; Awang, 1992; Mustafa et al., 1993; Kiuchi *et al.*, 1982; Ali *et al.*, 2008;	Chrubasik *et al.*, 2005; Ali *et al.*, 2008; Periera *et al.*, 2011 Baliga *et al*., 2011 Shirin Adel & Jamuna Prakash , 2010
	Vasala, 2004;	2. Connell and Sutherland, 1969; Yoshikawa *et al.*, 1993).	Govindarajan, 1982a, b; Yoshikawa *et al.*, 1993; Ali *et al.*, 2008. Shirin Adel & Jamuna Prakash , 2010	Butt and Sultan 2011.	

Anticancer Properties of Ginger

Ginger rich with many active components. The [6]-gingerol, a major pungent ingredient of ginger is a potent anti-angiogenic activity *in vitro* and *in vivo.* And [6]-gingerol may inhibit tumor growth and metastasis via its anti-angiogenic activity (Kim et al., 2005a,b). Topical application of [6]-gingerol inhibited COX-2 (cyclooxygenase-2) expression along with suppressed NF- kB DNA binding activity in mouse skin (Kim et al., 2004).

The proposed mechanisms of action of gingerol involved in anticancer and chemopreventive properties via multiple pathways that includes the inhibition of cyclooxygenase -2 (COX-2) expression by inhibiting p38 MAPK–NF-κB (mitogen activated protein kinase – necrosis factor kappa B) signaling pathway (Shukla and Singh, 2007). Ginger is a natural antioxidant and anticarcinogenic dietary component. The treatment with ginger on ovarian cancer cells *in vitro* revealed that inhibition in growth of cells effectively by 6- Shogaol and also inhibition of NF- kB activation and decreases VEGF (growth factor) and IL-8 secretion. Ginger components modulate secretion of angiogenic factors in ovarian cancer cells *in vitro* and act as potent chemopreventive dietary agent (Rhode *et al*, 2007).

A novel anticancer drug β- elemene is extracted from the ginger plant and it triggers apoptosis mediated through a mitochondrial release of the cytochrome c in non-small-cell lung cancer cells. The β-elemene induces caspase-3, -7 and -9 activities, decreases Bcl-2 expression, causes cytochrome c release and increases the levels of cleaved caspase-9 and poly (ADP-ribose) polymerase in cells (Wang *et al*., 2005). Enhanced enzyme activity of glutathione reductase (GR), glutathione peroxidase (GPX), glutathione -S- transferase (GST) leads to the suppression of colon carcinogenesis by ginger supplement. Ginger is very effectively reduces the colon cancer (Manju and Nalini, 2005).

Ginger and its component [6]- gingerol is effective against ovarian cancers *in –vivo*. Ginger inhibits necrosis factor kappa -B (NF-kB) and also interleukin- 8 (IL-8) inhibitions (Rhode *et al*., 2007). The [6]- gingerol is effective in suppressing growth of colon tumor in mice (Jeong *et al.*, 2009); [6]- gingerol acts against skin cancer (Nigam *et al.*, 2009); breast cancer (Lee *et al.*, 2008); ovarian cancer (Rhode *et al.*, 2007); [6]- gingerol and [6] shogals inhibits gastric cancer (Ishiguro *et al.*, 2007). The ginger constituents including [6] - shogaol, [6] - gingerol, [8] – gingerol and

[10]-gingerol were examined on humans to study pharmacokinetic properties of anticancer agents. (Zick *et al.*,2008). Another ginger compound [6]- paradol displays anticancer activity against skin cancer (Surh *et al.,* 1999).

Reduced the elevated expression of tumor necrosis factor - alfa (TNF-α) and NF-κB by extract ginger in liver cancer of rat (Habib *et al.,* 2008). The supplementation of ginger reduced lipid peroxidation and acts as an antioxidant via which it suppressed liver carcinogenesis (Yasmin Anum Mohd Yusof *et al.,* 2009). There are three ginger compounds include [6]-, [8]-, [10] - Shagaols are much stronger against tumor growth, observed in H-1299 human lung cancer cells and among these three [6]- Shagaol shows potential agent than [6]- gingerol (sang *et al.*,2009).

Growth of colon and lung cancer in mouse was suppressed and activates apoptosis by Zerumbone (Kim *et al.,* 2008); Zerumbone inhibits NF-kB activation in osteoclastogenesis in mouse (Sung *et al*., 2009); Zerumbone induces apoptosis in colon cancer and inhibits gasrtric cancers (Yodkeeree *et al*., 2009). There are two important target specific mechanisms in cancer therapy and they are telomerase inhibition and c-Myc inhibition. The ginger extract might prove to be a potential agent in cancer prevention and maintenance therapy (Tuntiwechapikul *et al*., 2010).

Anti-metastasis activity of 6-Shogaol was observed *in vitro* and 6-Shogaol is active against breast cancer (Ling et al., 2010).Study on the pharmacokinetic properties of anticancer agents identified from some of the important medicinal herbs was performed (Chen *et al.,* 2011). Two Bangladeshi ginger varieties (Fulbaria and Syedpuri) used to find out antioxidant and anticancer activities against MCF-7 and MDA-MB-231, two human breast cancer cell lines (Rahman *et al.*,2011).

Fresh ginger contains various phytochemicals with biological activities relevant in disease associated with reactive oxygen spicies (ROS). From the root bark of the fresh ginger, isolated about 29 phenolic compounds and their structures were fully characterized. They have examined the effect of these compounds against nine human tumor cell lines to study about their anticancer activity. The cytotoxic property in cell lines exhibited by three compounds, 6- shogaol, 10- gingerol and enone- diarylheptanoids analog of curcumin (Peng *et al.,* 2012). Terpenoids of ginger induces apoptosis by activation of p53 in an endometrial cancer cells (Yang Liu *et al.,* 2012), Ginger root effective on COX-1 in Colon cancer (Yan Jiang *et al* ., 2013). The major compound of ginger [6]-Shogaol are active in cancer cells (Yingdong Zhu *et al.,* 2013).

Table 2: Anticancer Activity of Ginger and Compounds of Ginger against Cancer

S. No	Compound Name	Cancer	Mechanism	Cell Lines/System	References
1	β-Elemene	non-small-cell lung cancer cells	release of cytochrome c	*In vitro*	Wang *et al*., 2005
2	Ginger – whole and [6]-gingerol.	Ovarian cancer	Inhibiton NF-κB ; tumor growth	*In vitro*	Rhode et al., 2007
3	Ginger extract	Liver cancer	Reduced the elevated expression of TNF-$\alpha$and NF-κB	rats.	Habib et al., 2008
4	[6]-gingerol	Breast cancer	Inhibits cell adhesion invasion motility	*In vitro*	Lee et al., 2008
		Skin cancer.	Enhances apoptotosis	Mouse	Nigam et al., 2009
		Colon cancer	Inhibition of leukotriene activity	mice	Jeong et al., 2009
5	Zerumbone	Lung and colon cancer	Suppresses modulatory mechanisms of growth and induce apoptosis. Reduces expression of NF-κB.	mouse	Kim et al., 2008

		Colon cancer	Activation of extracellular signal-regulated kinase 1/2 p38 mitogen-activated protein kinase.	*In vitro*	Yodkeeree et al., 2009
		Osteoclastogenesis.	Blocks NF-kappa B expression.	Mouse monocyte	Sung et al., 2009
6	6-Shogaol	Lungs cancer	Inhibition of AKT	*In vitro*	Hung et al., 2009
	6-Shogaol	Breast cancer	Anti-metastasis	*In vitro*	Ling et al., 2010
7	Ginger-flavonoids	Breast cancer	Antioxidant activity	*In vitro*	Rahman et al., 2011
8	Enone-diaryl heptanoid, 6-Shogaol, [10]-gingerol,	Liver/against nine human tumor cell (lines)	Inhibition of lipid peroxidation, Antioxidant activity, cytotoxic	*In vitro*	Peng et al., 2012
9	Terpenoids	Endometrial Cancer Cells	Induce Apoptosis by activation of p53	*In vitro*	Yang Liu *et al.*, 2012
10	[6]-Shogaol	Cancer cell	anticancer	*In vitro*	Yingdong Zhu *et al.*, 2013

CONCLUSIONS

Earlier research results conclude that ginger is an essential spice with many active principles. Ginger compounds involved in neutralizing many functions of a cell in unfavorable conditions, disease and cancer. The mechanism involved in the chemopreventive effects of ginger are contribute by free radical scavenging, antioxidant pathways, alteration of gene expressions and induction of apoptosis and thus cause decrease in tumor initiation, promotion and progression.

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